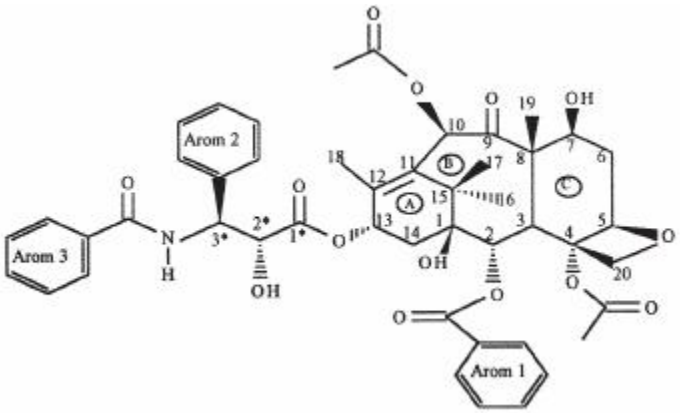
ONXOL - paclitaxel injection, solution, concentrate
IVAX Research, Inc.

WARNING

ONXOL® (paclitaxel) Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See "DOSAGE AND ADMINISTRATION" section). Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.
ONXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1,000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ONXOL.

DESCRIPTION

ONXOL® (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. ONXOL is available in 30 mg (5mL), 150 mg (25mL) and 300 mg (50mL) multiple dose vials. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of polyoxyl 35 castor oil, NF, 2 mg citric acid anhydrous and 49.7% (v/v) dehydrated alcohol, USP.
Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via an extractive process from Taxus brevifolia or Taxus yunnanensis. The chemical name for paclitaxel is (2#*R*,4S,4#*S*,6*R*,9*S*,11*S*,12*S*,12#*R*,12b*S*)-1,2#,3,4,4#,6,9,10,11,12,12#,12b-Dodecahydro-4,6,9,11,12,-12b-hexahydroxy-4#,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca [3,4] benz [1,2-*b*] oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.93. It is highly lipophilic, insoluble in water, and melts at around 216# - 217#C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
Following intravenous administration of paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3 and 24 hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

TABLE 1: SUMMARY OF PHARMACOKINETIC PARAMETERS – MEAN VALUES

DOSE (mg/m^2)	INFUSION DURATION (h)	N (patients)	C_{MAX} (ng/mL)	AUC (0-∞) (ng•h/ml)	T-HALF (h)	CL_T ($L/h/m^2$)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C_{MAX} = Maximum plasma concentration

AUC (0-∞) = Area under the plasma concentration – time curve from time 0 to infinity

CL_T = Total body clearance

It appeared that with the 24 hour infusion of paclitaxel, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{MAX} by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3 hour infusion, for a 30% increase in dose, the C_{MAX} and AUC (0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24 hour infusion of paclitaxel, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m^2 given by 1 hour infusions (n=15), 30 to 275 mg/m^2 given by 6 hour infusions (n=36), and 200 to 275 mg/m^2 given by a 24 hour infusions (n=54) in Phase 1 & 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicate that between 89-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m^2 doses of paclitaxel as 1, 6, or 24 hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m^2 dose of radio-labeled paclitaxel as a 3 hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6-α, 3'-p-dihydroxypaclitaxel by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See "PRECAUTIONS: Drug Interactions" section.) The effect of ranal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Ovarian Carcinoma

Second-Line Data: Data from five Phase 1 & 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of paclitaxel in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients), utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% Cl = 11% to 37%) and 30% (95% Cl = 18% to 46%) with a total of six complete and 18 partial responses in 92 patients. The median duration of overall response in these two studies measured from the first day of treatment was 7.2 months (range: 3.5 to 15.8 months) and 7.5 months (range: 5.3 to 17.4 months), respectively. The median survival was 8.1 months (range: 0.2 to 36.7 months) and 15.9 months (range: 1.8 to 34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of paclitaxel, administered at two different doses (135 or 175 mg/m^2) and schedules (3 or 24 hour infusion). The overall response rate for the 407 patients was 16.2% (95% Cl = 12.8% to 20.2%), with 6 complete and 60 partial responses. Duration of responses, measured from the first day of treatment was 8.3 months (range: 3.2 to 21.6 months). Median time to progression was 3.7 months (range: 0.1+ to 25.1+ months). Median survival was 11.5 months (range: 0.2 to 26.3 + months).

Response rates, median survival and median time to progression for the 4 arms are given in the following table:

TABLE 2: EFFICACY IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

	175/3 (n=96)	175/24 (n=106)	135/3 (n=99)	135/24 (n=106)
Response				
- rate (percent)	14.6	21.7	15.2	13.2
- 95% Confidence Interval	(8.5-23.6)	(14.5-31.0)	(9.0-24.1)	(7.7-21.5)
Time to Progression				
- median (months)	4.4	4.2	3.4	2.8
- 95% Confidence Interval	(3.0-5.6)	(3.5-5.1)	(2.8-4.2)	(1.9-4.0)
Survival				
- median (months)	11.5	11.8	13.1	10.7
- 95% Confidence Interval	(8.4-14.4)	(8.9-14.6)	(9.1-14.6)	(8.1-13.6)

Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the two doses (135 or 175 mg/m^2) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m^2 dose had a response rate similar to that of those receiving the 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3 hour with the 24 hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m^2 dose of paclitaxel had a longer time to progression than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months (p=0.03). The median time to progression for patients receiving the 3 hours vs. the 24 hour infusion was 4.0 months vs. 3.7 months respectively. Median survival was 11.6 months in patients receiving the 175 mg/m^2 dose of paclitaxel and 11.0 months in patients receiving the 135 mg/m^2 dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of paclitaxel and 11.2 months for patients receiving the 24-hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

Paclitaxel remained active in patients who had developed resistance to platinum containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, a platinum containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 & 2 clinical studies.

The adverse event profile in this Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in ten clinical studies. These adverse events and adverse events from the Phase 3 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 4 & 5) and narrative form.

The results of the randomized study support the use of paclitaxel injection at doses of 135 to 175 mg/m^2, administered by a 3 hour intravenous infusion. The same doses administered by 24 hour infusion were more toxic. However, the study had insufficient power to determine whether a particular dose and schedule produced superior efficacy.

Breast Carcinoma

After Failure of Initial Chemotherapy: Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of paclitaxel in patients with metastatic breast carcinoma.

Phase 2 Open Label Studies: Two studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. Paclitaxel was administered in these 2 trials as a 24 hour infusion at initial doses of 250 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response rates were 57% (95% Cl: 37% - 75%) and 52% (95% Cl: 32% - 72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of paclitaxel was 200 mg/m^2 as a 24 hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, for a response rate of 30% (95% Cl: 15% - 50%).

Phase 3 Randomized Study: This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive paclitaxel at a dose of either 175 mg/m^2 or 135 mg/m^2 given as a 3 hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% Cl: 22% - 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4 – 18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03 – 17.1 months). Median survival was 11.7 months (range: 0-18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table:
TABLE 3: EFFICACY IN BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

	175/3 (n=235)		**135/3 (n=236)**
Response			
- rate (percent)	28		22
- p-value		0.135	
Time to Progression			
- median (months)	4.2		3.0
- p-value		0.027	
Survival			
- median (months)	11.7		10.5
- p-value		0.321	

The adverse event profile of the patients who received single-agent paclitaxel in the phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 4 & 6) and narrative form.

INDICATIONS AND USAGE
ONXOL is indicated as subsequent therapy for the treatment of advanced carcinoma of the ovary.
ONXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS
ONXOL is contraindicated in patients who have a history of hypersensitivity reactions to ONXOL or other drugs formulated in polyoxyl 35 castor oil.
ONXOL should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1,000 cells/mm^3.

WARNINGS
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine and H_2 antagonists. (See "DOSAGE AND ADMINISTRATION" section.) Patients who experience severe hypersensitivity reactions to ONXOL should not be rechallenged with the drug.
Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. ONXOL should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (<1,000 cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be instituted during ONXOL treatment. Patients should not be re-treated with subsequent cycles of ONXOL until neutrophils recover to a level >1,500 cells/mm^3 (>1,000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.
Severe conduction abnormalities have been documented in <1% of patients during ONXOL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with ONXOL.
Pregnancy: ONXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality. There are no adequate and well controlled studies in pregnant women. If ONXOL is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS
Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may

be leached from PVC infusion bags or sets, diluted ONXOL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.
ONXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions

In a Phase 1 trial using escalating doses of paclitaxel (110 to 200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e. paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel injection was administered following cisplatin.
The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ONXOL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See "CLINICAL PHARMACOLOGY" section.)
Potential interactions between ONXOL, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.
Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology

ONXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ONXOL. Patients should not be retreated with subsequent cycles of ONXOL until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ONXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing polyoxyl 35 caster oil, (e.g. cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with ONXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with ONXOL should be pre-medicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of ONXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with ONXOL.

Cardiovascular

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel injection but generally do not require treatment. Occasionally ONXOL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of ONXOL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See "WARNINGS" section.)

Nervous System

Although, the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of ONXOL.
ONXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See "PRECAUTIONS: Pediatric Use" section.)

Hepatic

There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering ONXOL to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., "recall", has been reported rarely.
Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of paclitaxel has not been studied. ONXOL has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test of CHO/HGPRT gene mutation assay.
Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity (See WARNINGS section).

Pregnancy
Pregnancy Category D. (See "WARNINGS" section.)

Nursing Mothers
It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ONXOL therapy.

Pediatric Use
The safety and effectiveness of ONXOL in pediatric patients have not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

INFORMATION OF PATIENTS
(See PATIENT INFORMATION LEAFLET).

ADVERSE REACTIONS

Pooled Analysis of Adverse Events Experiences from Single-Agent Studies
Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent paclitaxel injection. Two hundred and seventy five patients were treated in eight Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six patients with breast carcinoma received paclitaxel (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

TABLE 4: SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT PACLITAXEL

		Percent of Patients (n=812)
Bone Marrow		
- Neutropenia	$<2,000/mm^3$	90
	$<500/mm^3$	52
- Leukopenia	$<4,000/mm^3$	90
	$<1,000/mm^3$	17
- Thrombocytopenia	$<100,000/mm^3$	20
	$<50,000/mm^3$	7
- Anemia	<11g/dL	78
	<8g/dL	16
- Infections		30
- Bleeding		14

- Red Cell Transfusions	25
- Platelet Transfusions	2
Hypersensitivity Reaction[b]	
- All	41
- Severe †	2
Cardiovascular	
- Vital Sign Changes [c]	
- Bradycardia (N=537)	3
- Hypotension (N=532)	12
- Significant Cardiovascular Events	1
Abnormal ECG	
- All Pts	23
- Pts with normal baseline (N=559)	14
Peripheral Neuropathy	
- Any	60
- Severe symptoms †	3
Myalgia/Arthralgia	
- Any	60
- Severe symptoms †	8
Gastrointestinal	
- Nausea and vomiting	52
- Diarrhea	38
- Mucositis	31
Alopecia	87
Hepatic (pts with normal baseline and on study data)	
- Bilirubin elevations (N=765)	7
- Alkaline phosphate elevations (N=575)	22
- AST (SGOT) elevations (N=591)	19
Injection Site Reaction	13

[a] Based on worst course analysis

[b] All patients received premedication

[c] During first 3 hours of infusion

† Severe events are defined as at least Grade III toxicity

None of the observed toxicities were clearly influenced by age.

Disease Specific Adverse Event Experiences

Second-Line Ovary: For the 403 patients who received single-agent paclitaxel in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

TABLE 5: FREQUENCY[a] OF ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

		PERCENT OF PATIENTS			
		175/3[b] (n=95)	**175/24[b] (n=105)**	**135/3[b] (n=98)**	**135/24[b] (n=105)**
Bone Marrow					
- Neutropenia	<2,000/mm^3	78	98	78	98
	<500/mm^3	27	75	14	67
- Thrombocytopenia	<100,000/mm^3	4	18	8	6

	<50,000/mm^3	1	7	2	1
- Anemia	<11g/dL	84	90	68	88
	<8g/dL	11	12	6	10
- Infections		26	29	20	18
Hypersensitivity Reaction[c]					
- All		41	45	38	45
- Severe †		2	0	2	1
Peripheral Neuropathy					
- Any symptoms		63	60	55	42
- Severe symptoms †		1	2	0	0
Mucositis					
- Any symptoms		17	35	21	25
- Severe symptoms †		0	3	0	2

[a] Based on worst course analysis

[b] Paclitaxel dose in mg/m^2/infusion duration in hours

[c] All patients received premedication

† Severe events are defined as at least Grade III toxicity

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

Breast Cancer After Failure of Initial Chemotherapy: For the 458 patients who received single-agent paclitaxel in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a-3 hour infusion).

TABLE 6: FREQUENCY[a] OF ADVERSE EVENTS IN THE PHASE 3 STUDY OF BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

		PERCENT OF PATIENTS	
		175/3 [b] (n=229)	**135/3 [b] (n=229)**
Bone Marrow			
- Neutropenia	<2,000/mm^3	90	81
	<500/mm^3	28	19
- Thrombocytopenia	<100,000/mm^3	11	7
	<50,000/mm^3	3	2
- Anemia	<11g/dL	55	47
	<8g/dL	4	2
- Infections		23	15
- Febrile Neutropenia		2	2
Hypersensitivity Reaction[c]			
- All		36	31
- Severe †		0	<1
Peripheral Neuropathy			
- Any symptoms		70	46

- Severe symptoms †	7	3
Mucositis		
- Any symptoms	23	17
- Severe symptoms †	3	<1

[a] Based on worst course analysis

[b] Paclitaxel dose in mg/m^2/infusion duration in hours

[c] All patients received premedication

† Severe events are defined as at least Grade III toxicity

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

Adverse Event Experiences By Body System

The following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in clinical studies. The frequency and severity of important adverse events for the phase 3 ovarian carcinoma and breast carcinoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from post-marketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving paclitaxel for the treatment of ovarian or breast carcinoma.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 ovarian study with a 3 hour infusion, neutrophil counts declined below 500 cells/mm^3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27% at a dose of 175 mg/m^2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 or 175 mg/m^2 given as a 3 hour infusion respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm^3). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel injection dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no patients treated with the 3 hour infusion received platelet transfusions.

Anemia (Hb<11 g/dL) was observed in 78% of all patients and was severe (Hb<8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all the patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to paclitaxel injection (See “WARNINGS” and “PRECAUTIONS: Hypersensitivity Reactions” sections). The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 second-line ovarian study the 3 hour infusion was not associated with a greater increase in HSRs when compared to the 24 hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period. Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most

often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.
Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.
Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.
Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See PRECAUTIONS: “Drug Interactions” section).
Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.
Respiratory: Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.
Neurologic: The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy.
The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34 to 51% from course 2 to 10.
Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.
Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia and neuroencephalopathy.
Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.
Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of paclitaxel and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.
Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.
Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.
Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24 hour than with the 3 hour infusion.
Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.
Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., “recall”, has been reported rarely.
Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.
A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to paclitaxel related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.
Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash and pruritus have been received as part of the continuing surveillance of paclitaxel safety. Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.
Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

OVERDOSAGE

There is no known antidote for ONXOL overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (See PRECAUTIONS: Pediatric Use section).

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted ONXOL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.
All patients should be premedicated prior to ONXOL administration in order to prevent severe hypersensitivity reactions.
Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before ONXOL, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to ONXOL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before ONXOL.
For patients with **carcinoma of the ovary**, the following regimen is recommended: In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel has been used at several doses and schedules, however, the optimal regimen is not yet clear (See CLINICAL STUDIES: Ovarian Carcinoma section). The recommended regimen is paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over three hours every three weeks.
For patients with **carcinoma of the breast**, the following regimen is recommended. (See CLINICAL STUDIES: Breast Carcinoma section): After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy paclitaxel at a dose of 175 mg/m^2 administered intravenously over three hours every three weeks has been shown to be effective.
For the therapy of patients with solid tumors (ovary and breast), courses of ONXOL should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during ONXOL (paclitaxel) Injection therapy should have dosage reduced by 20% for subsequent courses of ONXOL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.
Preparation and Administration Precautions: ONXOL is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling ONXOL. The use of gloves is recommended. If ONXOL solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If ONXOL contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.
Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (See “PRECAUTIONS: Injection Site Reaction” section).
Preparation for Intravenous Administration: ONXOL must be diluted prior to infusion. ONXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer’s Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.
Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. ONXOL solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.
ONXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of ONXOL since they can cause the stopper to collapse resulting in loss of sterile integrity of the ONXOL solution.
Stability: Unopened vials of ONXOL are stable until the date indicated on the package when stored between 20#-25#C (68#-77#F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the ONXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25#C) and lighting conditions for up to 27 hours.

HOW SUPPLIED
NDC 0172-3754-73 ONXOL (paclitaxel) Injection is available as a 30 mg/5 mL multi-dose vial individually packaged in a carton.
NDC 0172-3756-75 ONXOL (paclitaxel) Injection is available as a 150 mg/25 mL multi-dose vial individually packaged in a carton.
NDC 0172-3753-77 ONXOL (paclitaxel) Injection is available as a 300 mg/50 mL multi-dose vial individually packaged in a carton.
Storage: Store the vials in original cartons between 20#-25#C (68#-77#F). Retain in the original package to protect from light.
Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.

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6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.

7. Controlling Occupational Exposure of Hazardous Drugs (OSHA WORK-PRACTICE GUIDELINES). Am J Health – Syst-Pharm 1996; 53:1669-1685.

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PATIENT INFORMATION

ONXOL® (paclitaxel) Injection
(generic name **= paclitaxel)**

What is ONXOL® Injection?
Paclitaxel is a prescription cancer medicine, it is injected into a vein and it is used to treat different types of tumors. The tumors include advanced ovary and breast cancer.

What is cancer?
Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.
A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding health body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

How does ONXOL Injection work?
ONXOL Injection is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.
All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. ONXOL may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ONXOL causing some of the side effects. (See What are the possible side effects of paclitaxel? below.)

Who should not take ONXOL?
Patients who have a history of hypersensitivity (allergic reactions) to ONXOL or other drugs containing polyoxyl 35 castor oil, like cyclosporine or teniposide, should not be given ONXOL. In addition, ONXOL should not be given to patients with dangerously low white blood cell counts.

How is ONXOL Injection given?
ONXOL is injected into a vein (intravenous (IV) infusion). Before you are given ONXOL, you will have to take certain medicines (premedications) to prevent or reduce the chance you will have a serious allergic reaction. Such reactions have occurred in a small number of patients while receiving paclitaxel and have been rarely fatal. (See What are the possible side effects of paclitaxel? below.)

What are the possible side effects of paclitaxel?
Most patients taking paclitaxel will experience side effects, although it is not always possible to tell whether such effects are caused by paclitaxel, another medicine they may be taking, or the cancer itself. Important side effects are described below; however some patients may experience other side effects that are less common. Report any unusual symptoms to your doctor.
Important side effects observed in studies of patients taking paclitaxel were as follows:
allergic reactions. Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during paclitaxel infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash. The likelihood of a serious allergic reaction is lowered by the use of several kinds of medicines that are given to you before the paclitaxel infusion.
heart and blood vessel (cardiovascular) effects. Paclitaxel may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. Your heart function, including blood pressure and pulse, will be monitored while you are receiving the medicine. You should notify your doctor if you have a history of heart disease.
infections due to low white blood cell count. Among the body's defenses against bacterial infections are white blood cells. Between your paclitaxel treatment cycles, you will often have blood tests to check your white blood cell counts. Paclitaxel usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4° F) or other signs of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cells counts are low.*
hair loss. Complete hair loss, or alopecia, almost always occurs with paclitaxel. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your paclitaxel treatment.*
joint and muscle pain. You may get joint and muscle pain a few days after your paclitaxel treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.
irritation at the injection site. Paclitaxel sometimes causes irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself) and ulceration (open sores). These reactions are usually caused by the IV (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*
low red blood cell count. Red blood cells deliver oxygen to tissues throughout all part of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following paclitaxel treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following paclitaxel treatment.
mouth or lip sores (mucositis). Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the paclitaxel treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

numbness, tingling, or burning in the hands and/or feet (neuropathy). These symptoms occur often with paclitaxel and usually get better or go away without medication within several months of completing treatment. However, if you are uncomfortable, tell your doctor so that he/she can decide the best approach for relief of your symptoms.

stomach upset and diarrhea. Some patients experience nausea, vomiting, and/or diarrhea following paclitaxel use. If you experience nausea or stomach upset, tell your doctor. Diarrhea will usually disappear without treatment; however, *if you experience **severe** abdominal or stomach area pain and/or **severe** diarrhea, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with paclitaxel, it is important to talk with your doctor about other possible side effects.

Can I take ONXOL if I am pregnant or nursing a baby?

ONXOL could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with paclitaxel. Tell your doctor if you become pregnant or plan to become pregnant while taking ONXOL. Because studies have shown paclitaxel to be present in the breast milk of animals receiving the drug, it may be present in human breast milk as well. Therefore, nursing a baby while taking paclitaxel is NOT recommended.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about paclitaxel. Medications are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about paclitaxel, your doctor or pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

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